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FORM 1

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

F Hoffmann-La Roche & Co Aktiengesellschaft, of Grenzacherstrasse 124-184, 4002 Basle, SWITZERLAND, hereby apply for the grant of a standard patent for an invention entitled:

Acyl Derivatives

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
138410	US	28 December 1987
255004	US	7 October 1988

The address for service is:-

Spruson & Ferguson
Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia

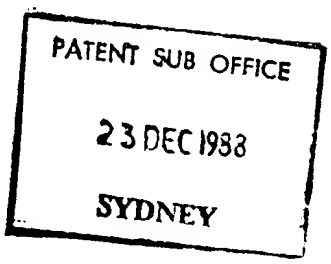
DATED this TWENTY SECOND day of DECEMBER 1988

F Hoffmann-La Roche & Co Aktiengesellschaft

By: 

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 80457
S&F CODE: 55541



5845/3

AUSTRALIA CONVENTION STANDARD & PETTY PATENT DECLARATION

RAN 4410/215

COMMONWEALTH OF AUSTRALIA

THE PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

Title of Invention: Acyl Derivatives

I Fridolin Klausner

Full name(s) and address(es) of Declarant(s): of 187 Baselmattweg, 4123 Allschwil, Switzerland

do solemnly and sincerely declare as follows:-

Full name(s) of Applicant(s)

1. I am authorised by F.HOFFMANN-LA ROCHE & CO. Aktiengesellschaft, of 124-184 Grenzacherstrasse, Basle, Switzerland,

the applicant~~(s)~~ for the patent to make this declaration on its/~~their~~ behalf.

2. The basic application(s) as defined by Section 141 of the Act ~~was~~/were made

Basic Country(ies): in U.S.A.

Priority Date(s): on December 28, 1987 and October 7, 1988

Basic Applicant(s): by ☐ F. HOFFMANN-LA ROCHE & CO., Aktiengesellschaft

both ☒ the inventor(s) cited in paragraph 3.

3.

Full name(s) and address(es) of inventor(s)

1) Ka-Kong Chan, 33 Charles Street, Hopatcong, N.J. 07843, U.S.A.

2) Dennis Dalton Keith, 8 Mendl Terrace, Montclair, N.J. 07042, U.S.A.

~~(respectively)~~

~~is~~/are the actual inventor(s) of the invention and the facts upon which the applicant~~(s)~~ is/~~are~~ entitled to make the application are as follows:

Set out how Applicant(s) derive title from actual inventor(s) e.g. The Applicant(s) is/are the assignee(s) of the invention from the inventor(s).

(X) the inventor(s) have assigned the invention to Hoffmann-La Roche Inc., Nutley, USA, who have re-assigned all their rights for Australia to the Applicant.

( ) the Applicant is the assignee of the invention from the inventor(s).

4. The basic application(s) referred to in paragraph 2 of this Declaration ~~was~~/were the first application(s) made in a Convention country in respect of the invention(s) the subject of the application.

Declared at Basle, Switzerland this 28th day of November, 1988

Fridolin Klausner

To:

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

(12) PATENT ABSTRACT (11) Document No. AU-A-27554/88
(19) AUSTRALIAN PATENT OFFICE

(54) Title
3(HETEROCYCLYC CARBONYL THIO METHYL)CEPHALOSPORIN DERIVATIVES

(51)[4] International Patent Classification(s)
C07D 501/36 C07D 519/00 A61K 031/545

(21) Application No. : 27554/88 (22) Application Date : 23.12.88

(30) Priority Data

(31) Number	(32) Date	(33) Country
138410	28.12.87	US UNITED STATES OF AMERICA
255004	07.10.88	US UNITED STATES OF AMERICA

(43) Publication Date : 29.6.89

(71) Applicant(s)
F. HOFFMANN-LA ROCHE & CO. AKTIENGESELLSCHAFT

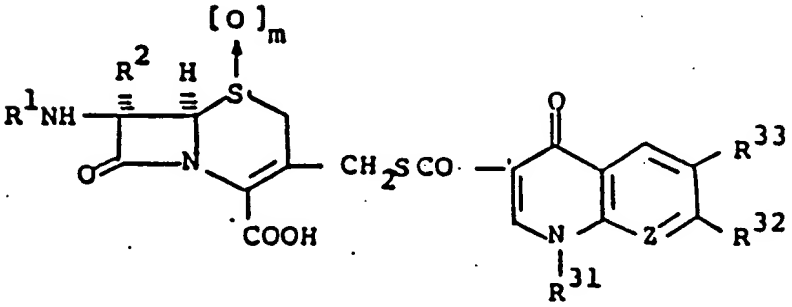
(72) Inventor(s)
NAME NOT GIVEN

(74) Attorney or Agent
SPRUSON & FERGUSON

(57) Claim

Antimicrobial pharmaceuticals.

1. Acyl derivatives of the formula



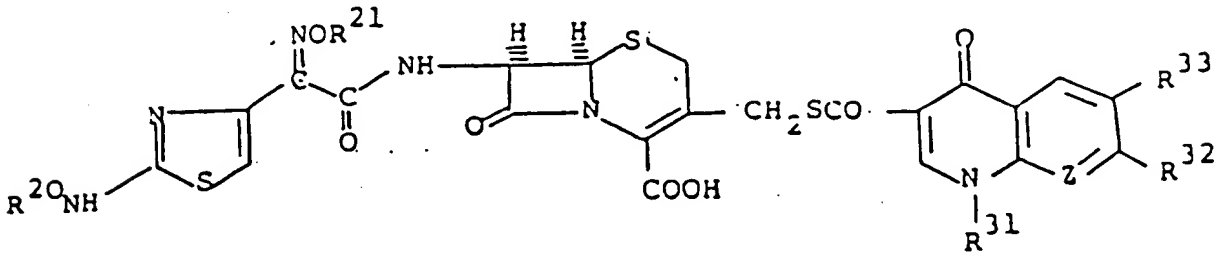
I

wherein m is zero, 1 or 2, R^1 is hydrogen or an acyl group; R^2 is hydrogen, lower alkoxy, lower alkylthio or lower alkanoylamino; R^{31} is hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl, phenyl or mono-, di- or tri-halo-phenyl; Z is R^{30}-C or nitrogen; R^{30} is hydrogen or halogen, or R^{30} and R^{31} when taken together represent a C_3-C_5 alkylene group, a C_2-C_4 alkylene mono- xy group or a C_1-C_2 alkylene dioxy group; R^{32} is hydrogen, halogen, lower alkyl or an optionally substituted 5- or 6-membered

nitrogen and/or sulphur atoms; and R^{33} is hydrogen or halogen, or R^{32} and R^{33} when taken together represent a C_1-C_4 alkylene dioxy group,

and the readily hydrolyzable esters or salts of these compounds and hydrates of the compounds of formula I or of their esters or salts.

11. A compound as in claim 1 of the formula



Ib

wherein R^{21} has the meaning given in claim 9 and Z, R^{31}, R^{32} and R^{33} have the meaning given in claim 1.

S & F Ref: 80457

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name and Address of Applicant: F Hoffmann-La Roche & Co Aktiengesellschaft
Grenzacherstrasse 124-184
4002 Basle
SWITZERLAND

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

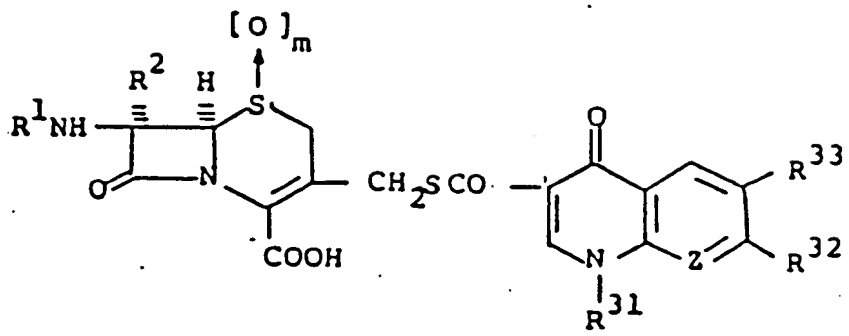
Acyl Derivatives

The following statement is a full description of this invention, including the best method of performing it known to me/us

RAN 4410/215

Abstract

The invention is concerned with acyl derivatives of the formula



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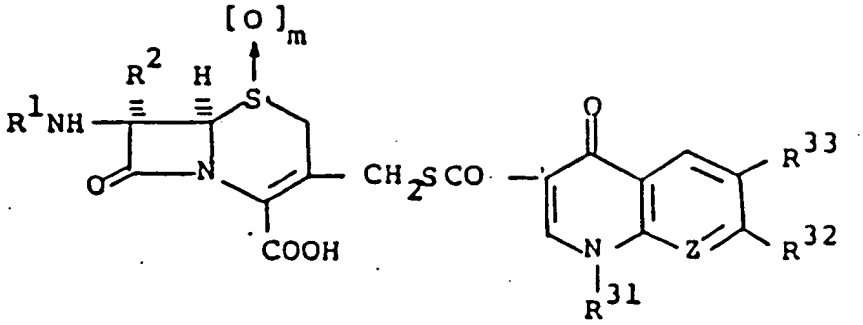
wherein m is zero, 1 or 2, R^1 is hydrogen or an acyl group; R^2 is hydrogen, lower alkoxy, lower alkylthio or lower alkanoylamino; R^{31} is hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl, phenyl or mono-, di- or tri-halo-phenyl; Z is R^{30}-C or nitrogen; R^{30} is hydrogen or halogen, or R^{30} and R^{31} when taken together represent a C_3-C_5 alkylene group, a C_2-C_4 alkylene mono-oxy group or a C_1-C_2 alkylene dioxy group; R^{32} is hydrogen, halogen, lower alkyl or an optionally substituted 5- or 6-membered heterocyclic ring containing one, two or three oxygen, nitrogen and/or sulphur atoms; and R^{33} is hydrogen or halogen, or R^{32} and R^{33} when taken together represent a C_1-C_4 alkylene dioxy group,

and th readily hydrolyzable esters or salts of these compounds and hydrat s of the compounds of formula I or of their esters or salts.

Also included is a process for the manufacture of these compounds as well as pharmaceutical preparations containing them.

The products have antimicrobial activity.

The present invention relates to acyl derivatives of the formula



I

wherein m is zero, 1 or 2, R^1 is hydrogen or an acyl group; R^2 is hydrogen, lower alkoxy, lower alkylthio or lower alkanoylamino; R^{31} is hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl, phenyl or mono-, di- or tri-halo-phenyl; Z is R^{30}-C or nitrogen; R^{30} is hydrogen or halogen, or R^{30} and R^{31} when taken together represent a C_3-C_5 alkylene group, a C_2-C_4 alkylene mono-oxy group or a C_1-C_2 alkylene dioxy group; R^{32} is hydrogen, halogen, lower alkyl or an optionally substituted 5- or 6-membered heterocyclic ring containing one, two or three oxygen, nitrogen and/or sulphur atoms; and R^{33} is hydrogen or halogen, or R^{32} and R^{33} when taken together represent a C_1-C_4 alkylene dioxy group,

and the readily hydrolyzable esters or salts of these compounds and hydrates of the compounds of formula I or of their esters or salts.

In the above formula I m is preferably 0.

As used in this specification, the term "lower alkyl" or "alkyl" refers to both straight and branched chain saturated hydrocarbon groups having 1 to 8 and Preferably, 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, iso-propyl, t-butyl and the like.

As used herein, the term "lower alkoxy" or "alkoxy" refers to a straight or branched chain hydrocarbonoxy groups wherein the "alkyl" portion is a lower alkyl group as defined hereinbefore. Exemplary are methoxy, ethoxy, n-propoxy and the like.

The term "halo" or "halogen" as used herein represents all four forms thereof, i.e. chloro, bromo, iodo or fluoro unless otherwise specified.

By the term "aryl" is meant a substituted or unsubsituted aromatic moiety, such as phenyl, tolyl, xylyl, mesityl, cumenyl, naphthyl and the like, wherein said aryl group may have 1 to 3 suitable substituents, such as halo (e.g. fluoro, chloro, bromo), hydroxy and the like.

By the term "lower alkanoyl" or "alkanoyl" as utilized herein is intended a moiety of the formula

$$R^{25}\text{-CO-}$$

wherein R^{25} is hydrogen or C_1 to C_6 alkyl. Exemplary of such groups are acetyl, formyl, propionyl, n-butyryl and the like.

By the term "substituted phenyl" is meant phenyl, mono- or di-substituted by halo (e.g. chloro, bromo, fluoro), lower alkyl, amino, nitro or trifluoromethyl.

By the term "substituted alkyl" is meant a "lower alkyl" moiety substituted by, for example, halo (e.g. chloro, fluoro, bromo), trifluoromethyl, amino, cyano, etc.

By the term "lower alkenyl" or "alkenyl" is meant a straight or branched chain hydrocarbon group which contains an olefinic double bond having 2 to 6 carbon atoms, i.e. the radical of compounds of the formula C_nH_{2n} wherein n is 2 to 6, e.g. allyl, vinyl, etc.

By the term "aralkyl" is meant a hydrocarbon group having both aromatic and aliphatic structures, that is, a hydrocarbon group in which a lower alkyl hydrogen atom is substituted by a monocyclic aryl group, e.g. by phenyl, tolyl, etc.

The expression "5-, 6- or 7-membered heterocyclic ring containing 1-4 oxygen, nitrogen and/or sulfur atoms" is intended to represent e.g. a 6-membered nitrogen-containing hetero ring such as pyridyl, piperidyl, piperidino, N-oxido--pyridyl, pyrimidyl, piperazinyl, pyridazinyl, N-oxido--pyridazinyl, etc., a 5-membered nitrogen-containing hetero ring such as pyrrolidinyl, pyrazolyl, imidazolyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl, etc., and others. Each of these hetero rings may be further substituted and, as the substituents, there may be mentioned, for example, lower alkyls such as methyl, ethyl, n-propyl, etc., lower alkoxys such as methoxy, ethoxy, etc., halogens such as chlorine, bromine, etc., halogen substituted lower alkyls such as trifluoromethyl, trichloroethyl, etc., amino, mercapto, hydroxy, carbamoyl or carboxy etc.

By the term "cyclo-lower-alkyl" or "cycloalkyl" is meant a 3-7 membered saturated carbocyclic moiety, e.g. cyclo-

propyl, cyclobutyl, cyclohexyl, etc.

R^{30} and R^{31} can together mean "C_3-C_5 alkylene", e.g. $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5$ or $-CH(CH_3)-(CH_2)_2-$; or also "C_2-C_4 alkylene mono-oxy", e.g. $-(CH_2)_2-O-$, $-(CH_2)_3-O-$, $-(CH_2)_4-O-$ or $-CH(CH_3)-CH_2-O-$; or alternatively "C_1-C_2 alkylene dioxy", e.g. $-O-CH_2-O-$, $-O-(CH_2)_2-O-$ or $-O-CH(CH_3)-O-$. Preferably a 5- or 6-membered condensed ring is formed. R^{32} and R^{33} can together mean "C_1-C_4 alkylene dioxy", e.g. $-O-CH_2-O-$, $-O-(CH_2)_2-O-$, $-O-(CH_2)_3-O-$, $-O-(CH_2)_4-O-$, $-O-CH(CH_3)-O-$, $-O-CH(CH_3)-CH(CH_3)-O-$ or the like. Preferably a 5- or 6-membered condensed ring is formed.

The term "acyl", as used in conjunction with R^1 herein, means and includes all organic radicals derived from an organic acid (i.e., a carboxylic acid) by removal of the hydroxy group. Although the group R^1 may be any one of many acyl radicals, certain acyl groups are preferred.

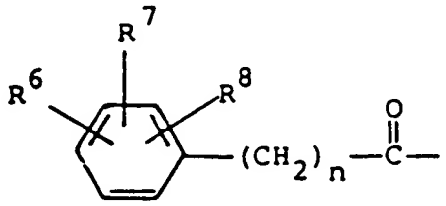
Exemplary acyl groups are those acyl groups which have been used in the past to acylate ß-lactam antibiotics including 6-aminopenicillanic acid and derivatives and 7-aminocephalosporanic acid and derivatives; see, for example, Cephalosporins and Penicillins, edited by Flynn, Academic Press (1972), Belgian patent 866,038 published October 17, 1978, Belgian patent 867,994, published December 11, 1978, United States patent 4,152,432, issued May 1, 1979, United States patent 3,971,778, issued July 27, 1976, and United States patent 4,173,199, issued October 23, 1979. The portions of these references describing various acyl groups are incorporated herein by reference. The following list of acyl groups is presented to further exemplify the term "acyl"; it should not be regarded as limiting that term. Exemplary acyl groups are:

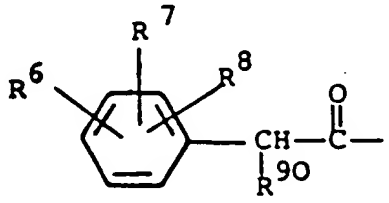
(a) Aliphatic groups having the formula

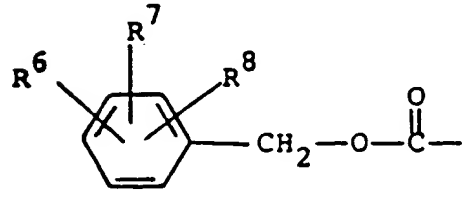
$$R^5\text{-}CO\text{-}$$

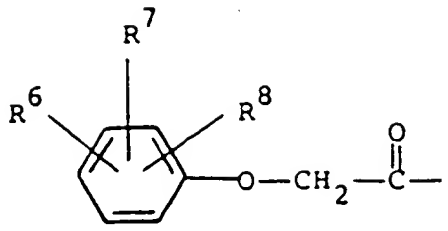
wherein R^5 is lower alkyl, C_3-C_7 cycloalkyl, lower alkoxy, lower alkenyl, C_3-C_7 cycloalkenyl or cyclohexadienyl; or lower alkyl or lower alkenyl substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, or cyanomethylthio groups.

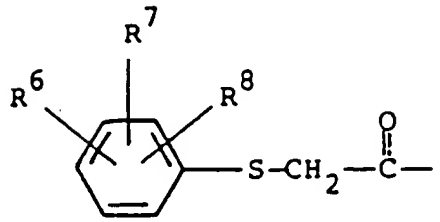
(b) Carbocyclic aromatic groups having one of the formulas

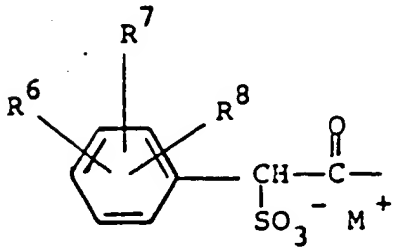


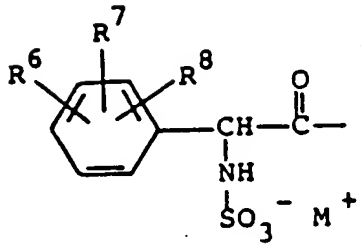






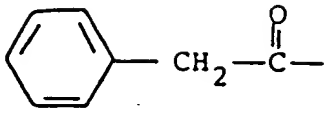


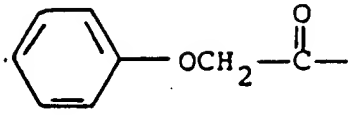


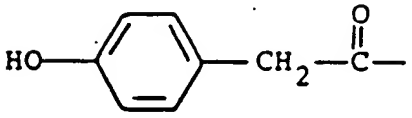


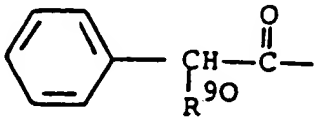
wherein n is 0, 1, 2 or 3; R^6, R^7 and R^8 each is independently hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or aminomethyl; and R^{90} is amino, acylamino, hydroxy, a carboxy salt, protected carboxy, such as benzyloxycarbonyl, formyloxy or azido; and M is a cation.

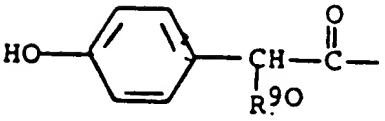
Preferred carbocyclic aromatic acyl groups include those having the formulas











(R^{90} ist pr ferably an amino group, a hydroxy group, or a carboxy salt or sulfo salt).

Examples of other acyl groups suitable for the purposes of the present invention are
sulfophenylacetyl,
hydroxysulfonyloxyphenylacetyl,
sulfamoylphenylacetyl,
(phenoxycarbonyl)phenylacetyl,
(p-tolyloxycarbonyl)phenylacetyl,
formyloxyphenylacetyl,
carboxyphenylacetyl,
formylaminophenylacetyl,
benzyloxycarbonylphenylacetyl,
2-(N,N-dimethylsulfamoyl)-2-phenylacetyl,
2-bromo-2-thienylacetyl, etc.

(c) Heteroaromatic groups having the formulas

$$R^{101}-(CH_2)_n-CO-$$

$$R^{101}-\underset{\displaystyle R^{90}}{\underset{|}{CH}}-CO-$$

$$R^{101}-O-CH_2-CO-$$

$$R^{101}-S-CH_2-CO-$$

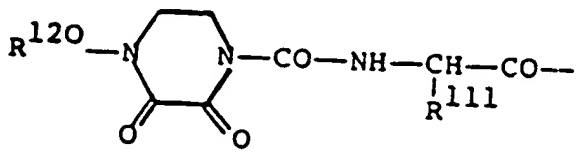
or

R^{101}-CO-CO-

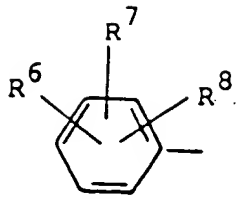
wherein n is 0, 1, 2 or 3; R^{90} is as defined above; and R^{101} is a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 (preferably 1 or 2) nitrogen, oxygen and/or sulfur atoms. Exemplary heterocyclic rings are thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl and tetrazolyl. Exemplary substituents are halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms or alkoxy of 1 to 4 carbon atoms.

Preferred heteroaromatic acyl groups include those groups of the above formulas wherein R^{101} is 2-amino-4--thiazolyl, 2-amino-5-halo-4-thiazolyl, 4-aminopyridin-2-yl, 2-amino-1,3,4-thiadiazol-5-yl, 2-thienyl, 2-furanyl, 4-pyridinyl or 2,6-dichloro-4-pyridinyl.

(d) [[(4-Substituted-2,3-dioxo -1-piperazinyl)carbonyl]-amino]arylacetyl groups having the formula



wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group (including carbocyclic aromatics) such as those of the formula



wherein R^6, R^7 and R^8 are as previously defined; or a heterocyclic ring as included within the definition of R^{101}; and R^{120} is lower alkyl or substituted lower alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino and/or mercapto groups), e.g. 4-lower alkyl (preferably ethyl or methyl)-2,3-dioxo-1-piperazinecarbonyl-D-phenylglycyl.

(e) (Substituted oxyimino)-arylacetyl groups having the formula

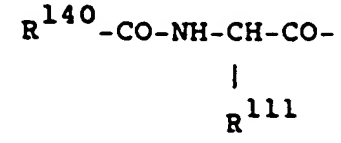
$$R^{130}\text{-O-N=C(}R^{101}\text{)-CO-}$$

wherein R^{101} is as defined above and R^{130} is hydrogen, lower alkyl, C_3-C_7 cycloalkyl, carboxy-C_3-C_7-cycloalkyl or substituted lower alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, aromatic group (as defined above by R^{111}), carboxy (including salts thereof), lower alkanoylamino, lower alkoxycarbonyl, phenylmethoxycarbonyl, diphenylmethoxycarbonyl, hydroxy-lower-alkoxyphosphinyl, dihydroxyphosphinyl, hydroxy-(phenylmethoxy)-phosphinyl or di-lower-alkoxyphosphinyl substituents).

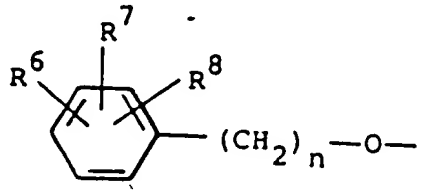
Examples of $R^{130}\text{-O-N=C(}R^{101}\text{)-CO-}$ grouping are

2-[(2-chloroacetamidothiazol-4-yl)]-2-[(p-nitrobenzyloxy-carbonyl)methoxyimino]acetyl, 2-(2-chloroacetamidothiazol-4--yl)-2-methoxyiminoacetyl, 2-(2-aminothiazol-4-yl)-2-isopropoxy-iminoacetyl, 2-(2-aminothiazol-4-yl)-2-methoxyimino-acetyl, 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetyl, 2-thienyl-2-methoxyiminoacetyl, 2-furyl-2-methoxyimino-acetyl, 2-(4-hydroxyphenyl)-2-methoxyiminoacetyl, 2-phenyl--2-methoxy-iminoacetyl, 2-phenyl-2-hydroxyiminoacetyl, 2-thienyl-2-hydroxyiminoacetyl, 2-thienyl-2-(dichloroacetyl-oxyimino)acetyl, 2-[4-(γ-D-glutamyloxy)phenyl]-2-hydroxy-iminoacetyl, 2-[4-(3-amino-3-carboxypropoxy)phenyl]-2--hydroxyiminoacetyl, 2-(5-chloro-2-chloroacetamidothiazol--4-yl) -2-methoxyiminoacetyl, 2-(5-chloro-2-aminothiazol-4--yl)-2-methoxyiminoacetyl, 2-[2-(t-butoxycarbonyl)isopro-poxyimino]-2-(2-sulfoamino -thiazol-4-yl)acetyl, 2-[2-(t-butoxycarbonyl)isopropoxyimino]-2 -(2-triphenyl--methylamino-thiazol-4-yl)acetyl, 2-(2-chloroacetamido-thiazol-4-yl)-2-isopropoxyiminoacetyl, 2-methoxyimino-2-(2--sulfoaminothiazol-4-yl)acetyl, 2-(2-aminothiazol-4-yl)-2--(carboxymethoxyimino)acetyl, 2-(2-mesylaminothiazol-4-yl)--2-isopropoxyiminoacetyl, 2-(2-imino-3-mesyl-4-thiazolin--4-yl)-2-isopropoxyiminoacetyl, 2-(2-aminothiazol-4-yl)-2--(carboxyisopropoxyimino)acetyl etc.

(f) (Acylamino) arylacetyl groups having the formula



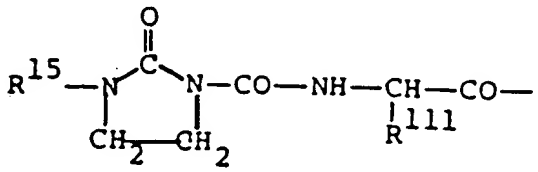
wherein R^{111} is as defined above and R^{140} is



(where R^6, R^7, R^8 and n are as previously defined), hydrogen, lower alkyl, substituted lower alkyl, amino, lower alkylamino, (cyanoalkyl)-amino or acylamino.

Preferred (acylamino) arylacetyl groups of the above formula include those groups wherein R^{140} is amino or acylamino. Also preferred are those groups wherein R^{111} is phenyl or 2-thienyl.

(g) [[[3-Substituted-2-oxo-1-imidazolidinyl]carbonyl]amino]-arylacetyl groups having the formula



wherein R^{111} is as defined above and R^{15} is hydrogen, lower alkylsulfonyl, arylmethyleneamino (i.e., $-N=CHR^{111}$ wherein R^{111} is as defined above), $R^{16}CO-$ (wherein R^{16} is hydrogen, lower alkyl or halogen substituted lower alkyl), an aromatic group (as defined by R^{111} above), lower alkyl or substituted lower alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino and/or mercapto groups).

Preferred [[[3-substituted-2-oxo-1-imidazolidinyl]carbonyl]amino]arylacetyl groups of the above formula include those wherein R^{111} is phenyl or 2-thienyl. Also preferred are those groups wherein R^{15} is hydrogen, methylsulfonyl, phenylmethyleneamino or 2-furylmethyleneamino.

In a preferred embodiment of the quinolonyl or azaquinolonyl substituent in 3-position Z is R^{30}-C wherein R^{30} is hydrogen, chlorine or fluorine, most preferably

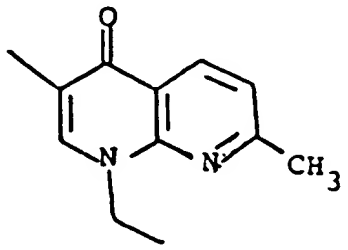
hydrogen or fluorine;

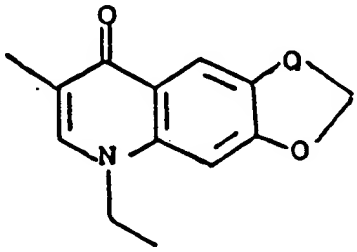
R^{31} is preferably lower alkyl, most preferably ethyl, or halogen-lower alkyl, most preferably fluoroethyl, or C_3-C_7-cycloalkyl, most preferably cyclopropyl;

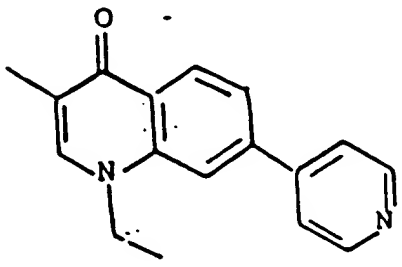
R^{32} is preferably lower alkyl, most preferably methyl, or piperazinyl which may be substituted on the 4-nitrogen atom with a lower alkyl group, most preferably methyl;

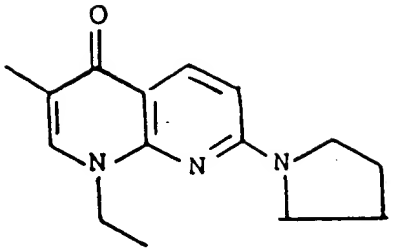
R^{33} is preferably hydrogen, chlorine or fluorine, more preferably hydrogen or fluorine, and still more preferably fluorine.

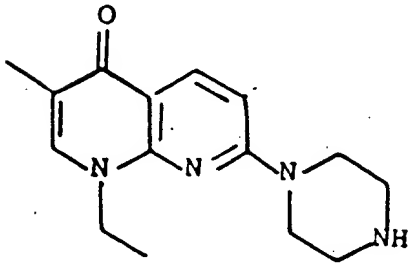
As used herein the quinolonyl or azaquinolonyl substituents in 3-position include, among others, groups of the formulas

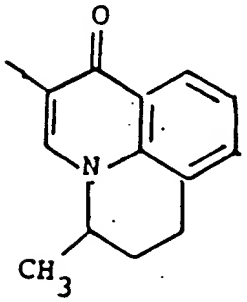


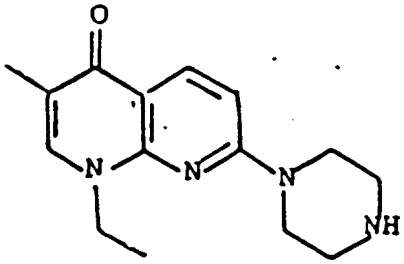


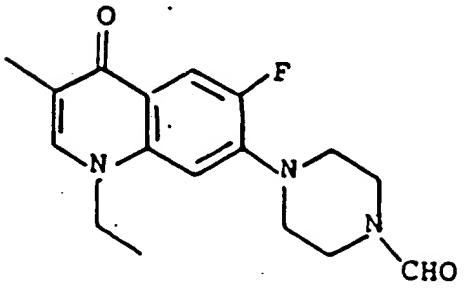


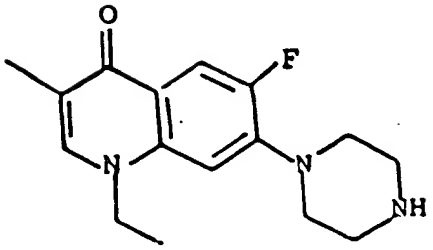


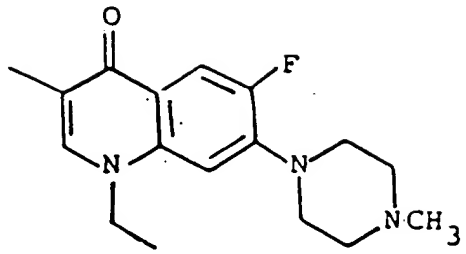


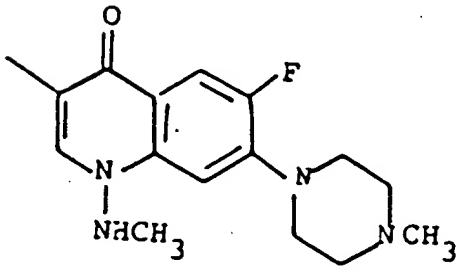


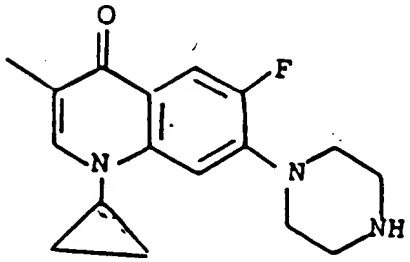


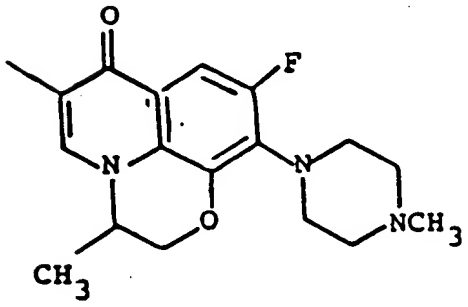


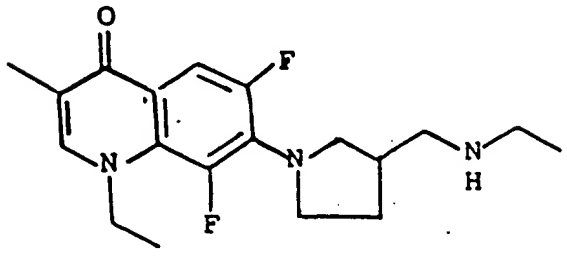


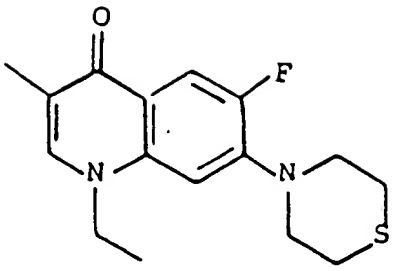


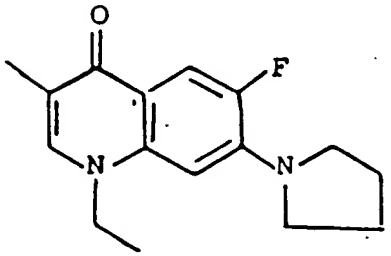


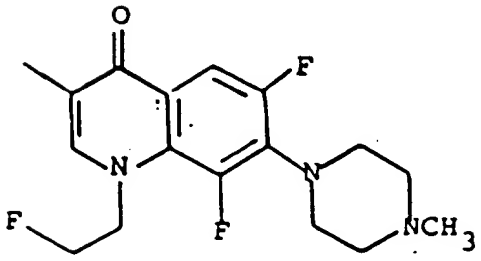


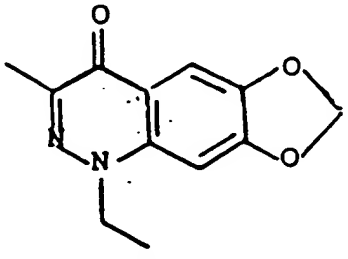


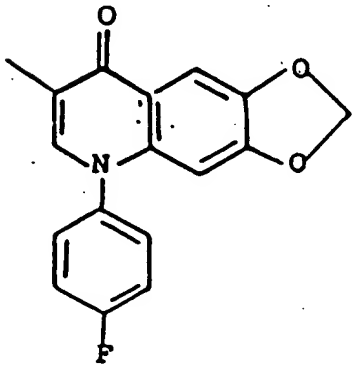


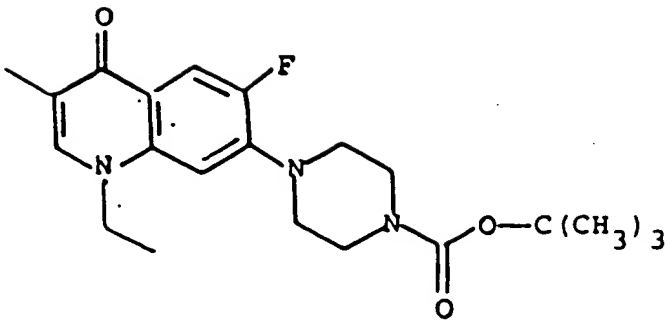


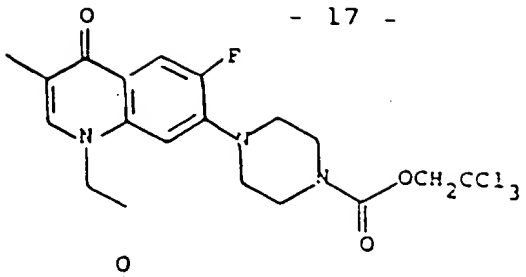


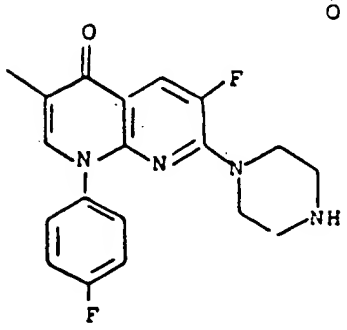


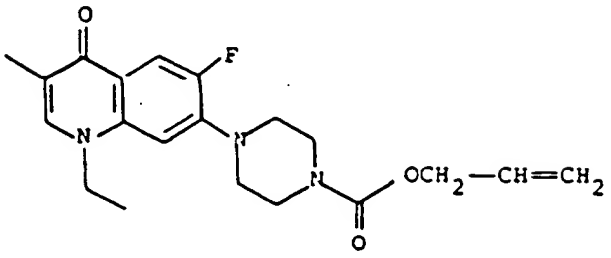


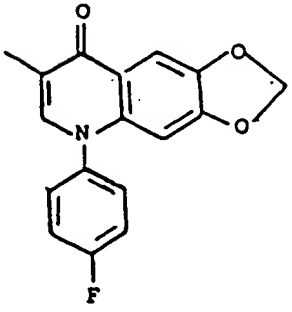


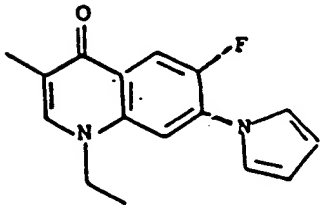


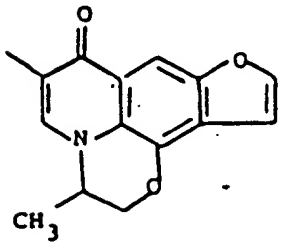


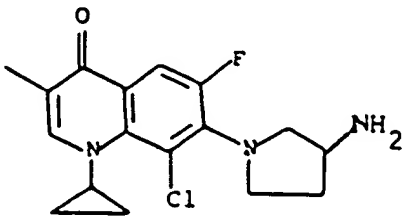




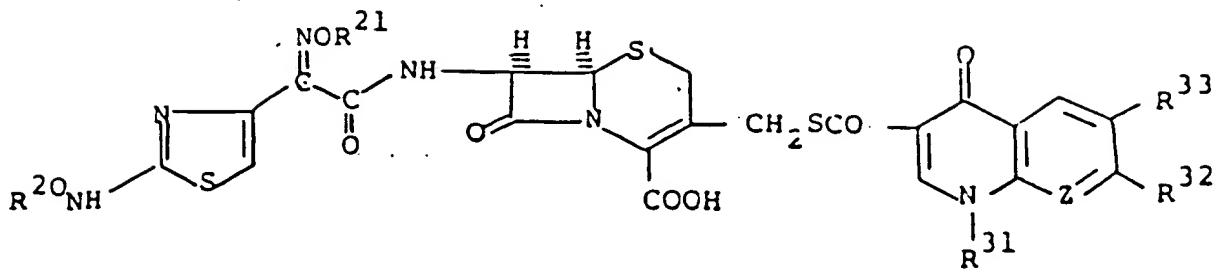




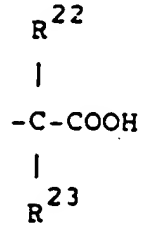




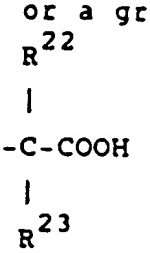
A preferred class of compounds are of the formula



wherein R^1 is as above, R^{20} is an amino protecting group such as trityl or chloroacetyl or, preferably, hydrogen. R^{21} is hydrogen, lower alkyl, or a group of the formula



wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and lower alkyl, or R^{22} and R^{23} taken together with the carbon atom to which they are attached form a 3-7 membered carbocyclic ring, e.g., cyclopropyl, cyclobutyl or cyclopentyl. Still more preferred are compounds of the formula Ib in which R^{20} is hydrogen and R^{21} is methyl or a group of the formula



wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and methyl.

Preferably, the $-C(=N-O-R^{130})-$ and $-C(=N-O-R^{21})-$ groupings are in the syn-form, i.e., the Z-form, or as mixtures in which the syn-form predominates.

As readily hydrolyzable esters of the compounds of formula I there are to be understood compounds of formula I, the carboxy group(s) of which (i.e. the 2-carboxy group and any other carboxy group present) is/are present in the form of readily hydrolyzable ester groups. Example of such esters, which can be of the conventional type, are the lower alkanoyloxyalkyl esters (e.g. the acetoxymethyl, pivaloyloxymethyl, 1-acetoxyethyl and 1-pivaloyloxyethyl ester), the lower alkoxycarbonyloxyalkyl esters (e.g. the methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester), the lactonyl esters (e.g. the phthalidyl and thiophthalidyl ester), the lower alkoxymethyl esters (e.g. the methoxymethyl ester) and the lower alkanoylaminomethyl esters (e.g. the acetamidomethyl ester). Other esters (e.g. the benzyl and cyanomethyl esters) can also be used.

Examples of salts of the compounds of formula I are alkali metal salts such as the sodium and potassium salt, the ammonium salt, alkaline earth metal salts such as the calcium salt, salts with organic bases such as salts with amines (e.g. salts with N-ethyl-piperidine, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, alkylamines or dialkylamines) as well as salts with amino acids such as, for example, salts with arginine or lysine.

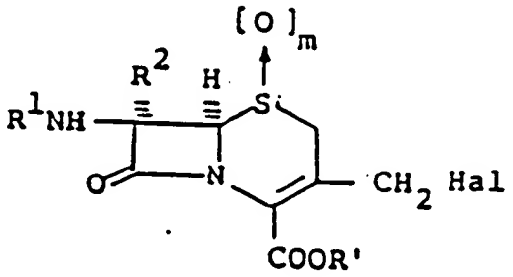
The compounds of formula I, when they contain a basic functional group such as an amine, also form addition salts with organic or inorganic acids. Examples of such salts are hydrohalides (e.g. hydrochlorides, hydrobromides and hydro-

iodides) as well as other mineral acid salts such as sulphates, nitrates, phosphates and the like, lower alkylsulphonates and monoarylsulphonates such as ethanesulfonates, toluenesulphonates, benzenesulphonates and the like and also other organic acid salts such as acetates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The compounds of formula I as well as their salts and readily hydrolyzable esters can be hydrated. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially anhydrous product.

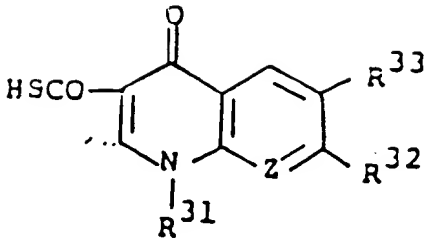
The acyl derivatives aforesaid are manufactured in accordance with the present invention by a process which comprises

(a) for the manufacture of an easily hydrolyzable ester of a carboxylic acid of formula I reacting a compound of the formula



II

wherein m, R^1 and R^2 are as above, Hal is halogen and R' is the residue of an easily hydrolyzable ester, with a salt of a carbothioic acid of the formula

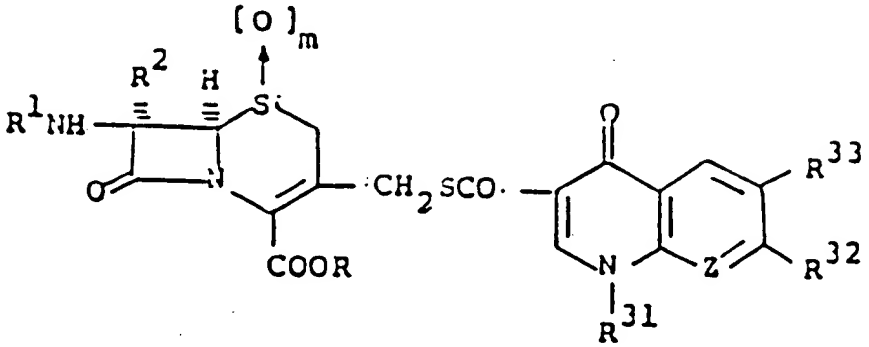


III

wherein R^{31}, R^{32} and R^{33} are as above,

or

(b) for the manufacture of a carboxylic acid of formula I converting an ester of the formula

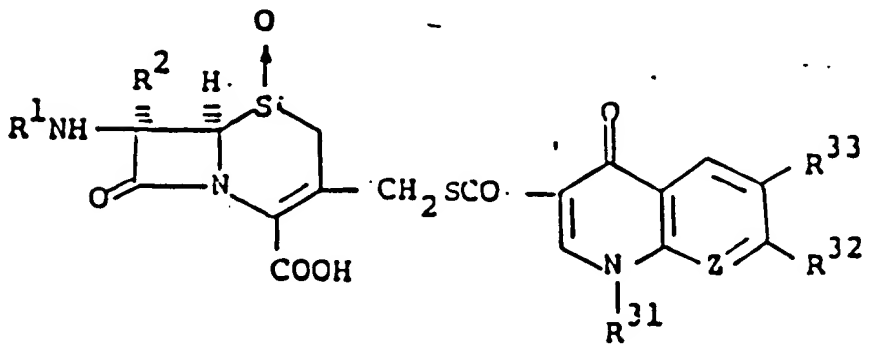


IV

wherein m, R^1, R^2, R^{31}, R^{32} and R^{33} are as above and R is an ester protecting group,

to the carboxylic acid of formula I, or

(c) for the manufacture of a compound of formula I, in which m is zero, reducing a compund of the formula

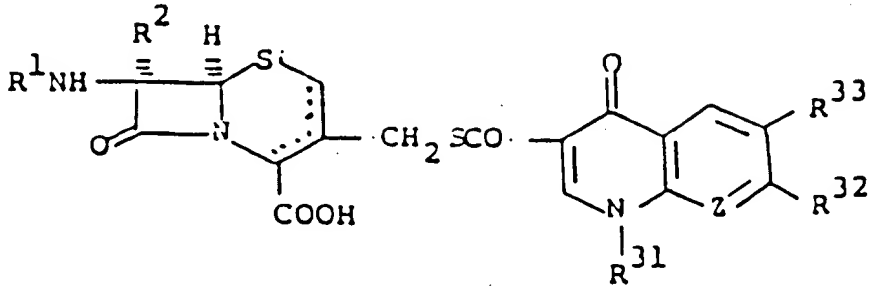


V

wherein R^1, R^2, R^{31}, R^{32} and R^{33} are as above,

or

(d) for the manufacture of a compound of formula I, in which m is 1 or 2, or an ester or salt thereof oxidizing a compound of the formula

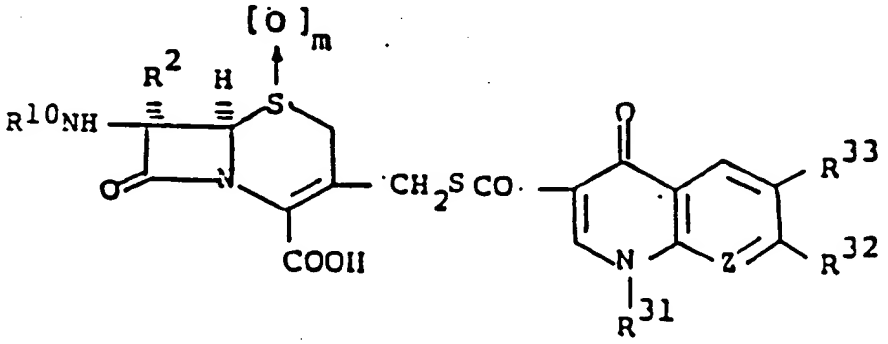


VI

wherein R^1, R^2, R^{31}, R^{32} and R^{33} are as above and the dotted lines indicate the presence of a Δ2 or Δ3 double bond,

or an ester or salt thereof, or

e) for the manufacture of a compound of formula I, in which R^1 contains an amino substituent, or an ester or salt thereof, cleaving off the amino-protecting group in the substituent R^{10} of a compound of the formula



VII

wherein m, R^2, R^{31}, R^{32} and R^{33} are as above and R^{10} is an acyl group containing a protected amino group,

or of an ester or salt thereof, or

(f) for the manufacture of a readily hydrolyzable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding esterification, or

(g) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts converting a compound of formula I into a salt or hydrate or into a hydrate of said salt.

The reaction of compounds II with the salts of compounds III according to embodiment (a) is preferably carried out in a nonhydroxylic solvent, such as, dimethylformamide, methylene chloride or N,N'-dimethylacetamide. Other nonhydroxylic solvents may also be utilized. Suitable salts of the quinolone acid are, for example, sodium, potassium, cesium, tetrabutylammonium or tetramethylammonium. Hal is a halogen, preferably bromine or iodine. The reaction is Preferably run at about 0°C to 80°C with about room temperature as preferred.

The deprotection of the esters IV according to embodiment (b) is effected using agents compatible with the ester protecting group utilized. As ester protecting groups R one may utilize an ester form which can be easily converted into a free carboxyl group under mild conditions, the ester protecting group being exemplified by, for example, t-butyl, p-nitrobenzyl, benzhydryl, allyl, etc. Also the residues of the readily hydrolyzable esters mentioned above as end products may be employed. For example the following reagents and their corresponding compatible esters are utilized: p-nitrobenzyl removed by hydrolysis in the presence of sodium sulfide at about or below 0°C to room temperature in a solvent, such as, dimethylformamide (aqueous); t-butyl removed by reaction with trifluoroacetic acid in the presence of anisole at about 0°C to room temperature with or without a co-solvent, such as methylene chloride; or allyl removed by a palladium (0) catalyzed transallylation reaction in the presence of sodium or potassium salt of 2-ethyl hexanoic acid, see for example J. Org. Chem. 1982, 47, 587.

The reduction of the sulfoxides V according to embodiment (c) is effected utilizing one of a variety of reactions, for example, treatment with phosphorus trichloride in dimethylformamide or trifluoroacetic anhydride in the presence of sodium iodide in acetone/methylene chloride. Both of the above reactions can be carried out at about 0°C to -20°C with about 0°C preferred.

The oxidation of the compounds VI according to embodiment (d) isomerizes any Δ2 isomer VI to the corresponding Δ3 isomer of formula I wherein n is 1 or 2. The oxidation is carried out by treatment with an organic or inorganic oxidizing agent. Various compounds which readily yield oxygen can be used as the oxidizing agent; for example, organic peroxides such as monosubstituted organic peroxides (e.g. C_1-C_4 alkyl- or alkanoylhydroperoxides such as

t-butylhydroperoxide), performic acid and peracetic acid, as well as phenyl-substituted derivatives of these hydroperoxides such as cumenehydroperoxide and perbenzoic acid. The phenyl substituent can, if desired, carry a further lower group (e.g. a C_1-C_4 alkyl or alkoxy group), a halogen atom or a carboxy group (e.g. 4-methylperbenzoic acid, 4-methoxy-perbenzoic acid, 3-chloroperbenzoic acid and monoperphthalic acid). Various inorganic oxidizing agents can also be used as the oxidizing agent; for example, hydrogen peroxide, ozone, permanganates such as potassium or sodium permanganate, hypochlorites such as sodium, potassium or ammonium hypochlorite, peroxymonosulphuric and peroxydisulphuric acid. The use of 3-chloroperbenzoic acid is preferred. The oxidation is advantageously carried out in an inert solvent, for example, in an aprotic inert solvent such as tetrahydrofuran, dioxan, methylene chloride, chloroform, ethyl acetate or acetone or in a protic solvent such as water, a lower alkanol (e.g. methanol or ethanol) or a lower alkanecarboxylic acid which may be halogenated (e.g. formic acid, acetic acid or trifluoroacetic acid). The oxidation is generally carried out at a temperature in the range of -20°C to +50°C.

When the oxidizing agent is used in equimolar amounts or in slight excess in relation to the starting material there is mainly obtained the corresponding sulfoxide, i.e. a compound of formula I in which m stands for 1. When the amount of oxidizing agent is increased to double the stoichiometric ratio or more, there is obtained the corresponding sulfone, i.e. a compound of formula I in which m stands for 2. It is also possible to obtain the sulfone from the corresponding sulfoxide by treatment with an equimolar or greater amount of the oxidizing agent. The process conditions are essentially the same as in the manufacture of the sulfoxides.

The cleavage of the amino-protecting group in the substituent R^{10} of a compound VII according to embodiment (e) gives corresponding compounds of formula I carrying a free amino group. Possible amino-protecting groups are those employed in peptide chemistry, such as an alkoxycarbonyl group, e.g., t-butoxycarbonyl, etc., a substituted alkoxycarbonyl group, e.g., trichloroethoxycarbonyl, etc., a substituted aralkyloxycarbonyl group, e.g., p-nitrobenzyloxycarbonyl, an aralkyl group such as trityl or benzhydryl or a halogen-alkanoyl group such as chloroacetyl, bromoacetyl, iodoacetyl or trifluoroacetyl.

Preferred protecting groups are t-butoxycarbonyl (t-BOC) and trityl.

The amino protecting groups may be cleaved off by acid hydrolysis (e.g. the t-butoxycarbonyl or trityl group) or by basic hydrolysis (e.g. the trifluoroacetyl group). The chloroacetyl, bromoacetyl and iodoacetyl groups are cleaved off by treatment with thiourea.

Amino-protecting groups which are cleavable by acid hydrolysis are preferably removed with the aid of a lower alkanecarboxylic acid which may be halogenated. In particular, formic acid or trifluoroacetic acid is used. The acid hydrolysis is generally carried out at room temperature, although it can be carried out at a slightly higher or slightly lower temperature (e.g. a temperature in the range of about 0°C to +40°C). Protecting groups which are cleavable under basic conditions are generally hydrolyzed with dilute aqueous caustic alkali at 0°C to 30°C. The chloroacetyl, bromoacetyl and iodoacetyl protecting groups can be cleaved off using thiourea in acidic, neutral or alkaline medium at about 0°C-30°C.

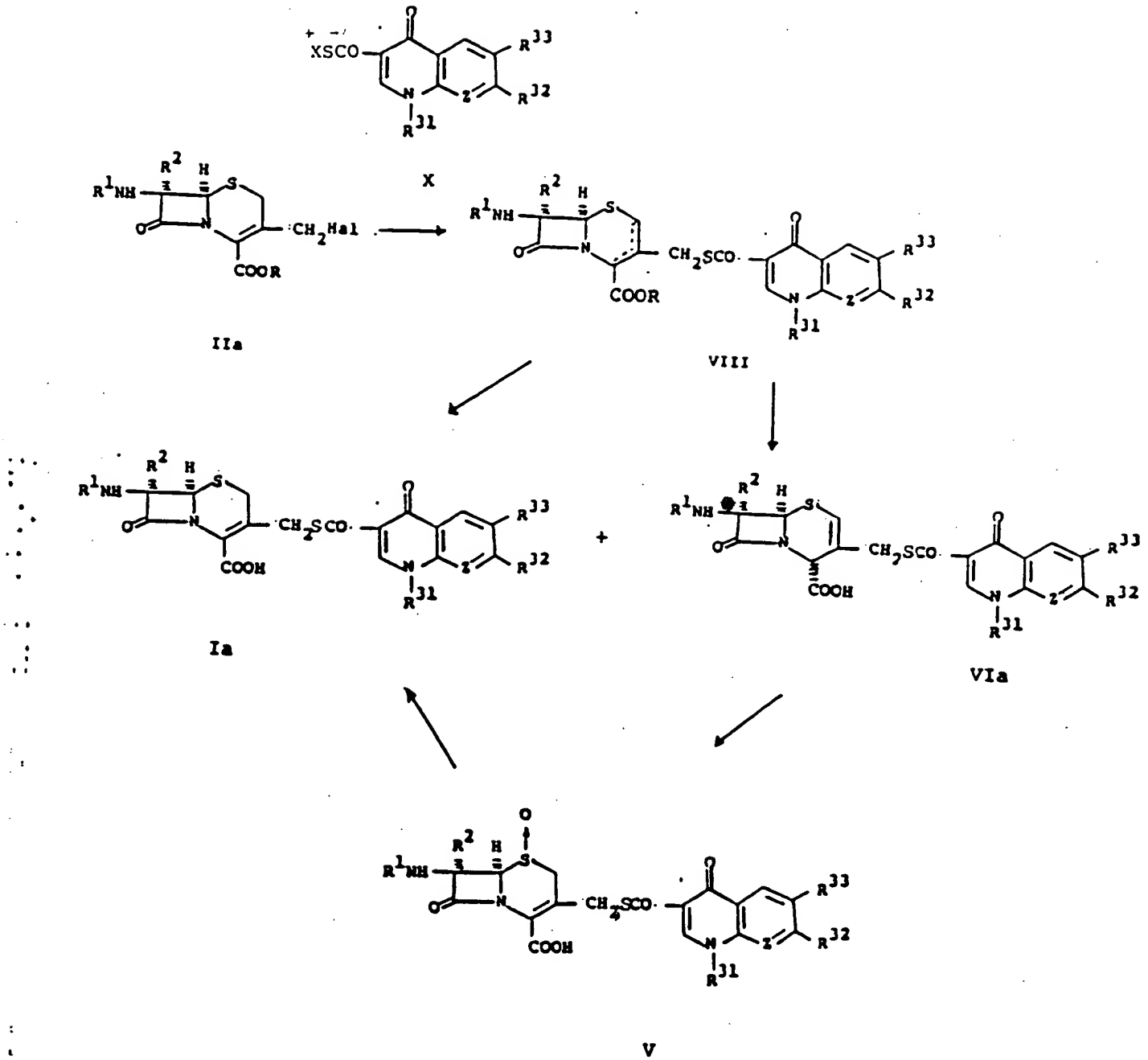
In order to manufacture a readily hydrolyzable ester of the carboxylic acids of formula I in accordance with embodiment (f) of the process provided by the present invention, a carboxylic acid of formula I is preferably reacted with a corresponding halide, preferably an iodide, containing the desired ester group. The reaction can be accelerated with the aid of a base such as an alkali metal hydroxide, an alkali metal carbonate or an organic amine such as triethylamine. The esterification is preferably carried out in an inert organic solvent such as dimethylacetamide, hexamethylphosphoric acid triamide, dimethyl sulfoxide or, especially, dimethylformamide. The reaction is preferably carried out at a temperature in the range of about 0°C-40°C.

The manufacture of the salts and hydrates of the compounds of formula I or the hydrates of said salts in accordance with embodiment (g) of the process provided by the present invention can be carried out in a manner known per se; for example, by reacting a carboxylic acid of formula I with an equivalent amount of the desired base, conveniently in a solvent such as water or an organic solvent (e.g. ethanol, methanol, acetone and the like). The temperature at which the salt formation is carried out is not critical. The salt formation is generally carried out at room temperature, but it can be carried out at a temperature slightly above or below room temperature, for example in the range of 0°C to +50°C.

The manufacture of the hydrates usually takes place automatically in the course of the manufacturing process or as a result of the hygroscopic properties of an initially anhydrous product. For the controlled manufacture of a hydrate, a completely or partially anhydrous carboxylic acid of formula I or salt thereof can be exposed to a moist atmosphere (e.g. at about +10°C to +40°C).

Examplary of the process for obtaining products in accordance with the invention is the following reaction scheme I:

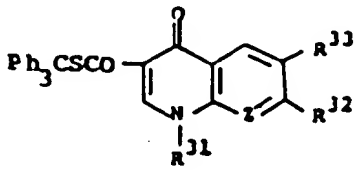
Scheme I



R^1, R^2, R^{31}, R^{32}, R^{33}, R, Z and the dotted bonds are all as defined above and X is a cation.

Scheme I

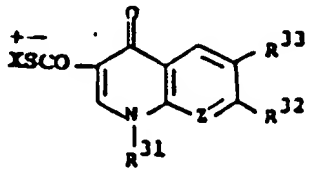
The carboxylic acid form of the corresponding quinolone was activated by treatment with 2-fluoro-1-methylpyridinium salt. Exposure of the activated acid to triphenylmethylmercaptan and 4-dimethylaminopyridine gave the thio ester of the formula



IX

wherein R^{31}, R^{32}, R^{33} and Z are as above and Ph is phenyl.

The compound of the formula IX was treated with an aqueous acid, preferably hydrochloric acid and then neutralized with a base, preferably potassium hydroxide, to give the thioic acid salt of the formula



X

wherein R^{31}, R^{32}, R^{33} and Z are as above and X^+ is a cation.

IIa → VIII

The compound of formula IIa which is known or made by analogy, see, for Example U.S. Patent No. 4,406,899 and U.S. Patent No. 4,266,049 is reacted with the salt of the chosen quinolone, viz, a compound of formula X. The reaction is carried out as described above for process alternative (a). Depending on the ester protecting group chosen and the halogen employed, the double bond in the cephem ring of the reaction product of formula VIII may be Δ3 or Δ2 with regard to the sulfur atom due to isomerization.

VIII → Ia and VIa

The compound of formula VIII thereafter is deprotected as described above for process alternative (b) resulting in a carboxylic acid of formula Ia or a mixture thereof with the Δ2 isomer of formula VIa.

VIa → V

If isomerization of the double bond occurs, the compound of formula VIa is thereafter oxidized as described for process alternative (d). e.g. with a peracid, such as metachloroperbenzoic acid, in a solvent, such as methylene chloride, at a reaction temperature of about -20°C to 40°C, preferably at about 0°C.

V → Ia

The compound of formula V is itself an end product falling under formula I. However, it can be reduced to an end product Ia as described above for process alternative (c).

Compounds of formula I containing the groupings

$$\begin{array}{c} N\text{-}O\text{-}R^{130} \\ \| \\ -C- \end{array} \qquad \text{or} \qquad \begin{array}{c} N\text{-}O\text{-}R^{21} \\ \| \\ -C- \end{array}$$

(cf. above) preferably exist as syn-forms. Such syn forms can be obtained by utilizing starting materials containing this grouping pre-formed in the syn-form. Alternatively, a syn/anti mixture obtained can be separated into the corresponding syn and anti forms in usual manner, e.g. by recrystallization or by chromatographical methods using a suitable solvent or solvent mixture.

Compounds of formula I, their salts and correspcnding hydrates and esters can be used as agents to combat bacterial infections (including urinary tract infections and respiratory infections) in mammalian species, e.g., dogs cats, horses, etc., and humans. These cephalosporins are antibacterially active and exhibit activity against a broad range of both gram-negative and gram-positive bacteria.

The in vitro activity of the compounds of the present invention as measured by the Minimum Inhibitory Concentration in micrograms/ml utilizing the Broth Dilution Method against a variety of Gram-positive and Gram-negative organisms can be represented by the following:

In vitro activity of [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-/-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monosodium salt trihydrate was as follows:

		MIC[a]	ED_{50}[b]
Escherichia coli	257	0.0625	<2
	DCO	0.125	
	DC_2	≤0.0157	
Pseudomonas aeruginosa	56	64	
Staphylococcus aureus	Smith	2	43
Streptococcus pneumoniae	6301	≤0.0157	

a) MIC in µg/ml
b) ED_{50} in mg/kg

For combatting bacterial infections in mammals, a compound of this invention can be administered to a mammal in need thereof in an amount of about 5 mg/kg/day to about 500 mg/kg/day, preferably about 10 mg/kg/day to 100 mg/kg/day, most preferably about 10 mg/kg/day to about 55 mg/kg/day.

All modes of administration which have been used in the past to deliver penicillins and cephalosporins to the site of the infection are also contemplated for use with the novel family of the dual action cephalosporins of this invention. Such methods of administration include intravenous, intramuscular and enteral administration.

The cephalosporin derivatives provided by the present invention can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier mat rial. This carrier material can be an organic or inorganic inert carrier material which is suitable for

enteral or parenteral administration such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkyleneglycols, petroleum jelly etc. The pharmaceutical preparations can be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). The pharmaceutical preparations may be sterilised and/or may contain adjuvants such as preserving, stabilising, wetting or emulsifying agents, salts for varying the osmotic pressure, anaesthetics or buffers. The pharmaceutical preparations can also contain other therapeutically valuable substances. The carboxylic acids of formula I as well as their salts and hydrates are especially suitable for parenteral administration and for this purpose they are preferably made up in the form of lyophilisates or dry powders for dilution with customary agents such as water or isotonic sodium chloride solution, as well as solvent mediators such as propylene glycol. The readily hydrolyzable esters of formula I are also suitable for enteral administration.

The following examples are illustrative but not limitative of the invention.

Example 1

A suspension of 2-fluoro-1-methylpyridinium p-toluenesulfonate (21.25 g, 0.075 mol) in dry dichloromethane (300 ml) was cooled to -15° to -10°C in an ice-salt bath and stirred under argon. To this mixture 6,8-difluoro-1-(2--fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo--3-quinoline carboxylic acid (22.16 g, 0.06 mol) and 4-dimethylaminopyridine (7.32 g, 0.06 mol) were added slowly at -10°C. The yellow reaction mixture was stirred at -10°C for 30 minutes and then tr ated with triphenylmethylmercaptan (16.6 g, 0.06 mol) and 4-dimethylaminopyridine

(7.32 g, 0.06 mol) at -20°C, the mixture was equilibrated slowly to 23°C and stirring was continued for 16 hours. It was diluted with CH_2Cl_2 (about 1.0 l). Concentration of solvent at reduced pressure yielded 45 g of yellow oil, which was purified twice by flash chromatography on silica gel (100 g) and eluted with 20% acetone in CH_2Cl_2. The fractions containing the desired product were combined and concentrated in vacuo to give 6,8-difluoro-1-(2-fluoroethyl)--1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarbothioic acid S-triphenylmethyl ester semihydrate.

Example 2

A mixture of 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro--7-(4-methyl-1-piperazinyl)-4-oxo-3-quinoline carbothioic acid S-triphenylmethyl ester semihydrate (6.1 g, 9.6 mmol) and aqueous 6N HCl (8 ml) in tetrahydrofuran (30 ml) was stirred at 23°C under argon for 16 hours. It was concentrated at 30°C and was then taken into water (50 ml) and $CHCl_3$ (50 ml). The mixture was treated with 1.0N KOH aqueous solution (about 55 ml) to pH about 11. It was extracted with $CHCl_3$ (2 x 50 ml). The combined $CHCl_3$ extracts were back extracted with water (2 x 50 ml). The organic extracts were dried ($MgSO_4$) and concentrated to give 2.57 g of foam which was shown by thin layer chromatography to be mostly the starting thioester. The combined aqueous phases were passed through a C_{18} reverse phase chromatography column (100 g) and eluted with a gradient of 3% to 20% acetonitrile-water. The fractions containing the desired product were combined and concentrated in vacuo to remove acetonitrile. The aqueous solution was lyophilized to give 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3--quinoline carbothioic acid potassium salt hydrate as a yellow solid.

Example 3

A mixture of 6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro--7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinoline carbothioic acid potassium salt hydrate (1.8 g, 4.07 mmol) and 2.0 g of propylene oxide in 20 ml of dry dimethylformamide was stirred at 23°C under argon. To this mixture a solution of [6R-[6α,7β(Z)]]-7-[[[[(methoxyimino)-2-(triphenylmethyl)-amino]-4-thiazolyl]acetyl]amino]-3-(iodomethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]- oct-2-ene-2-carboxylic acid t-butyl ester (3.69 g, 4.5 mmol) in dry CH_2Cl_2 (25 ml) was added and stirring was continued for 36 minutes under argon. The reaction mixture was taken into ethylacetate (100 ml) and washed with water (1 x 100 ml) and brine (2 x 100 ml). The aqueous washings were back extracted with ethyl acetate (2 x 100 ml). The organic extracts were combined, dried ($MgSO_4$) and filtered. The solvent was concentrated at reduced pressure to give 4.1 g of crude produce which was flash chromatographed on silica gel (125 g). Elution with 2% to 4% CH_3OH in $CHCl_3$ gave fractions 6 to 13 containing the desired product. Evaporation of solvent to dryness at reduced pressure afforded a tan solid: [6R-[6α,7β(Z)]]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-7-[[[[(methoxyimino)-2-(triphenylmethyl)amino]-4-thiazolyl]-acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1,1-dimethylethyl ester.

Example 4

A solution of [6R-[6α,7β(Z)]]-3-[[[[6,8-difluoro-1--(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4--oxo-3-quinolinyl]carbonyl]thio]methyl]-7-[[[[(methoxyimino)-2--(triphenylmethyl)amino]-4-thiazolyl]acetyl]amino]-8-oxo-5--thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid 1,1-dimethylethyl ester (1.9 g, 2.2 mmol), 2 ml of anisole, and 0.1 ml of 1,2-ethanedithiol in 20 ml of CH_2Cl_2 was cooled to 0°C and tr ated with 20 ml of cold trifluoroacetic

acid. The reaction mixture was kept at -20°C for 17 hours, and then evaporated in a rotary evaporator at about 4°C and at reduced pressure. The residue was taken into CH_2Cl_2 (10 ml), and ether (100 ml) was added quickly. The precipitate was collected and washed well with ether to yield 2.03 g of solid. This material was dissolved in 1:1 acetonitrile-H_2O (20 ml) and treated with 5% aqueous $NaHCO_3$ solution. During this process, dimethylformamide (5 ml) was added to dissolve the gummy material. More bicarbonate solution was added until the solution reached pH 9.0. The aqueous solution was then chromatographed on a reverse phase chromatography (C_{18} absorbent) column and eluted with 5% to 60% acetonitrile in water. Fractions 11-16 (eluted with 20% to 25% CH_3CN/H_2O) were combined, concentrated in vacuo, and then lyophilized to give the product as a white powder: [6R-[6α,7β(Z)]]-7--[[2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[[6,8--difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monosodium salt trihydrate.

Following the procedures set forth in the Examples, the following compounds are prepared:

[6R-(6α,7β)]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]-carbonyl]thio]methyl]-8-oxo-7-[(phenoxyacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)methoxyimino]-acetyl]amino]-3-[[[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[6R-(6α,7β)]-7-[(cyanoacetyl)amino]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid,

[6R-(6α,7β)]-7-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)-carbonyl]amino]phenylacetyl]amino]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid,

[6R-[6α,7β(Z)]]-8-[[(2-amino-4-thiazolyl)-[[(1-carboxy-1-methyl)ethoxy]imino]acetyl]amino]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[6R-[6α,7β(Z)]]-7-[[[(2-amino-4-thiazolyl)(carboxy-methoxy)imino]acetyl]amino]-3-[[[[6,8-difluoro-1-(2-fluoro-ethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid,

[6R-[6α,7β(Z)]]-7-[[[(2-amino-4-thiazolyl)methoxyimino]-acetyl]amino]-3-[[[[9-fluoro-3,7-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2H-pyrido[1,2,3-de]-1,4-benzoxazin-6-yl]-carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,

[6R-(6α,7β)]-α-[[[2-carboxy-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-7-yl]amino]carbonyl]benzeneacetic acid,

[6R-[6α,7β)]]-7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[6-fluoro-1-(4-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Example A

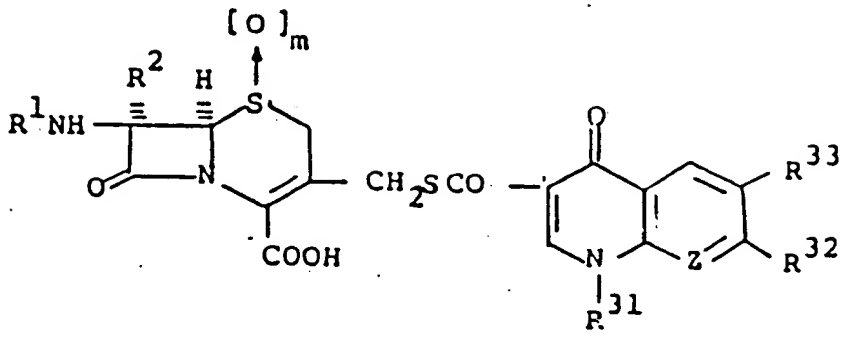
Production of dry ampoules for intramuscular administration:

A lyophilisate of 1 g of [6R-[6α,7β(Z)]]-7-[[2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monosodium salt trihydrate is prepared in the usual manner and filled into an ampoule. The sterile water ampoule contains 10% propylene glycol. Prior to the administration, the lyophilisate is treated with 2.5 ml of a 2% aqueous lidocaine hydrochloride solution.

~~Claims~~

The claims defining the invention are as follows:

1. Acyl derivatives of the formula



I

wherein m is zero, 1 or 2, R^1 is hydrogen or an acyl group; R^2 is hydrogen, lower alkoxy, lower alkylthio or lower alkanoylamino; R^{31} is hydrogen, lower alkyl, lower alkenyl, C_3-C_7 cycloalkyl, halo-lower alkyl, phenyl or mono-, di- or tri-halo-phenyl; Z is R^{30}-C or nitrogen; R^{30} is hydrogen or halogen, or R^{30} and R^{31} when taken together represent a C_3-C_5 alkylene group, a C_2-C_4 alkylene mono-oxy group or a C_1-C_2 alkylene dioxy group; R^{32} is hydrogen, halogen, lower alkyl or an optionally substituted 5- or 6-membered heterocyclic ring containing one, two or three oxygen, nitrogen and/or sulphur atoms; and R^{33} is hydrogen or halogen, or R^{32} and R^{33} when taken together represent a C_1-C_4 alkylene dioxy group,

and the readily hydrolyzable esters or salts of these compounds and hydrates of the compounds of formula I or of their esters or salts.

2. A compound as in claim 1 wherein m is zero and R^2 is hydrogen.

3. A compound as in claim 1 or 2, wherein Z is R^{30}-C, wherein R^{30} is hydrogen or halog n, R^{31} is lower alkyl, halo-lower alkyl or C_3-C_7 cycloalkyl, R^{32} is lower

alkyl, piperazinyl or lower alkylpiperazinyl and R^{33} is hydrogen or halogen.

4. A compound as in claim 3 wherein R^{30} is hydrogen or fluorine, R^{31} is ethyl, fluoroethyl or cyclopropyl, R^{32} is piperazinyl or 4-methylpiperazinyl, and R^{33} is hydrogen or fluorine.

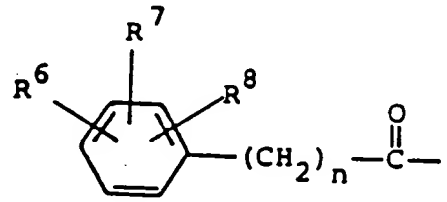
5. A compound as in any one of claims 1-4 wherein R^1 is an acyl group selected from the group consisting of

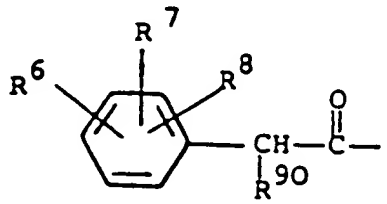
(a) an aliphatic group of the formula

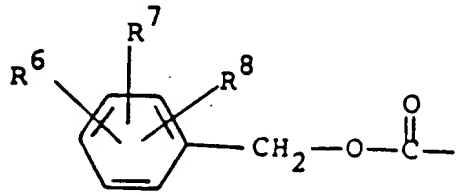
$$R^5\text{-}CO\text{-}$$

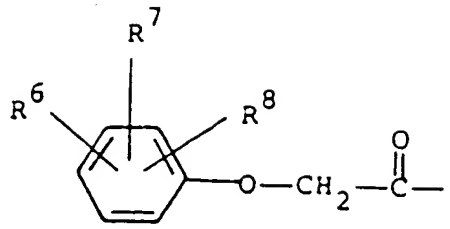
wherein R^5 is selected from the group consisting of lower alkyl, C_3-C_7 cycloalkyl, lower alkoxy, lower alkenyl, C_3-C_7 cycloalkenyl or cyclohexadienyl; or lower alkyl or lower alkenyl substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio or cyanomethylthio groups;

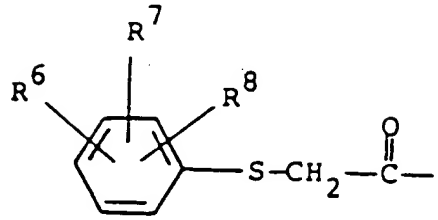
(b) a carbocyclic aromatic group selected from the group consisting of

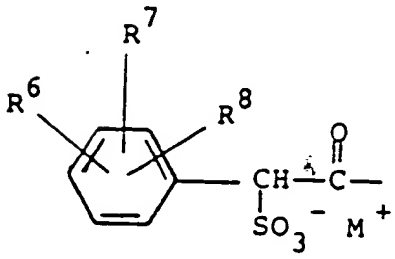


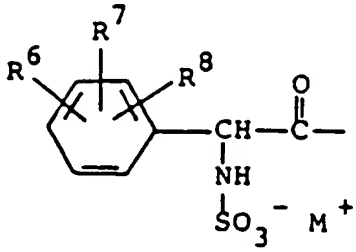












wherein n is 0, 1, 2 or 3; R^6, R^7 and R^8 each is independently selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or aminomethyl; and R^{90} is selected from the group consisting of amino, hydroxy, a carboxy salt, protected carboxy, formyloxy or azido; and M is a cation;

(c) a heteroaromatic group selected from the group consisting of

$$R^{101}-(CH_2)_n-CO-$$

$$R^{101}-CH(R^{90})-CO-$$

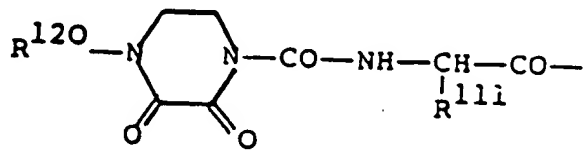
$$R^{101}-O-CH_2)-CO-$$

$$R^{101}-S-CH_2)-CO-$$

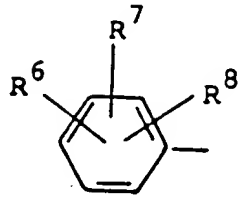
$$R^{101}-CO-CO-$$

wherein n is 0, 1, 2 or 3; R^{90} is as defined above; and R^{101} is a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 nitrogen, oxygen and/or sulfur atoms;

(d) a [[4-substituted-2,3-dioxo-1-piperazinyl)carbonyl]-amino]arylacetyl group of the formula

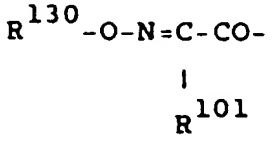


wherein R^{111} is lower alkyl, hydroxy-lower alkyl or an aromatic group of the formula



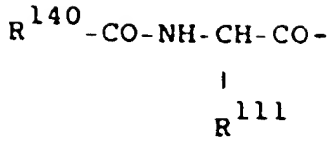
wherein R^6, R^7 and R^8 are as previously defined, or a heteroaromatic as defined for R^{101} and R^{120} is lower alkyl or substituted lower alkyl (wherein the alkyl group is substituted with one or more halogen, cyano, nitro, amino and/or mercapto groups);

(e) a (substituted oxyimino) arylacetyl group of the formula

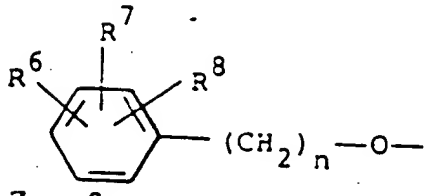


wherein R^{101} is as defined above and R^{130} is hydrogen, lower alkyl, C_3-C_7 cycloalkyl, carboxy-C_3-C_7-cycloalkyl or substituted lower alkyl (wherein the alkyl group is substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, aromatic group (as defined by R^{111}), carboxy (including salts thereof), lower alkanoylamino, lower alkoxycarbonyl, phenylmethoxycarbonyl, diphenylmethoxycarbonyl, hydroxyalkoxyphosphinyl, dihydroxyphosphinyl, hydroxy-(phenylmethoxy)-phosphinyl or di-lower alkoxy-phosphinyl substituents);

(f) an (acylamino) arylacetyl group of the formula

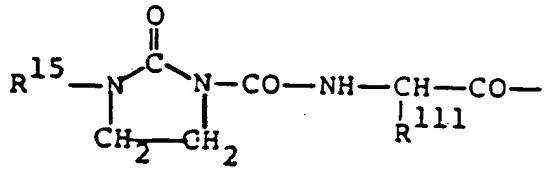


wherein R^{111} is as defined above and R^{140} is



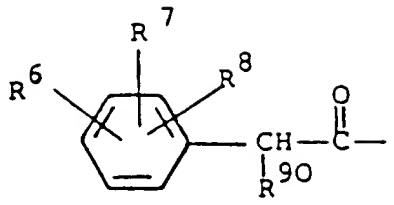
(whee R^6, R^7, R^8 and n are as previously defined) hydrogen, lower alkyl, substituted lower alkyl, amino, alkylamino, (cyanoalkyl) amino, or acylamino; and

(g) a [[[3-substituted-2-oxo-1-imidazolidinyl]carbonyl]-amino]arylacetyl group of the formula



wherein R^{111} is as defined above and R^{15} is hydrogen, alkylsulfonyl, $-N=CH-R^{111}$ (wherein R^{111} is as defined above), $R^{16}CO-$ (wherein R^{16} is hydrogen, alkyl or halogen substituted alkyl), an aromatic group (as defined by R^{111} above), lower alkyl or substituted lower alkyl (wherein the lower alkyl group is substituted with one or more halogen, cyano, nitro, amino and/or mercapto groups).

6. A compound as in any one of claims 1-4 wherein R^1 is an acyl group comprising a carbocyclic aromatic group of the formula



wherein R^{90} is selected from the group consisting of amino, acylamino, hydroxy, a carboxy salt, benzyloxycarbonyl, formyloxy and azido, and R^6, R^7 and R^8 are selected from the group consisting of hydrogen, halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, C_1-C_4 alkyl, C_1-C_4 alkoxy and aminomethyl.

7. A compound as in claim 7 wherein R^6, R^7, R^8 are hydrogen and R^{90} is hydrogen or hydroxy.

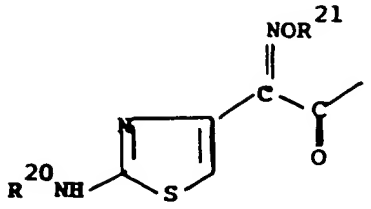
8. A compound as in any one of claims 1-4 wherein R^1 is an acyl group comprising a group of the formula

$$R^{130}\text{-O-N=C(R}^{101}\text{)-CO-}$$

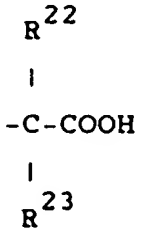
wherein R^{101} is an unsubstituted or substituted 5-, 6- or 7-membered heterocyclic ring containing 1, 2, 3 or 4 nitrogen, oxygen and/or sulfur atoms wherein the heterocyclic ring may be substituted by halogen, hydroxy, nitro, amino, cyano, trifluoromethyl, C_1-C_4 alkyl or C_1-C_4 alkoxy and R^{130} is hydrogen, lower alkyl, C_3-C_7 cycloalkyl, carboxy-C_3-C_7-cycloalkyl or substituted lower alkyl, wherein the lower alkyl is substituted with one or more halogen, cyano, nitro, amino, mercapto, lower alkylthio, aromatic group (as defined by R^{111} in claim 5), carboxy (including salts thereof), lower alkanoylamino, lower alkoxycarbonyl, phenylmethoxcarbonyl, diphenylmethoxycarbonyl, hydroxy-lower-alkoxphosphinyl, dihydroxyphosphinyl,

hydroxy(phenylmethoxy)phosphinyl or di-lower-alkoxyphosphinyl.

9. A compound as in any one of claims 1-4 wherein R^1 is an acyl group of the formula

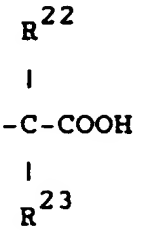


wherein R^{20} is hydrogen or an amino protecting group R^{21} is hydrogen, lower alkyl or a group of the formula



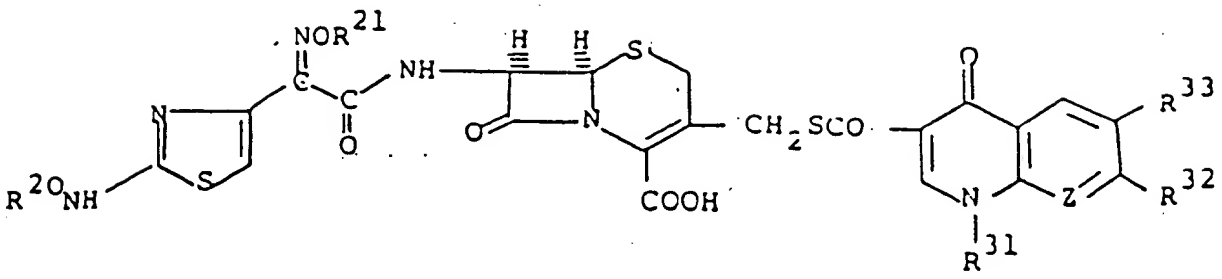
wherein R^{22} and R^{23} are selected rom the group consisting of hydrogen, lower alkyl or taken together with the carbon atom to which they are attached form a 3-7-membered carbocyclic ring.

10. A compound as in claim 9 wherein R^{20} is hydrogen, R^{21} is methyl or



wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and methyl.

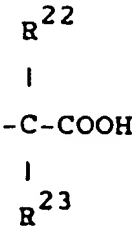
11. A compound as in claim 1 of the formula



Ib

wherein R^{21} has the meaning given in claim 9 and Z, R^{31}, R^{32} and R^{33} have the meaning given in claim 1.

12. A compound as in claim 11 wherein R^{21} is methyl or a group of the formula

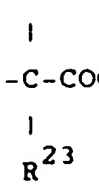


wherein R^{22} and R^{23} are hydrogen or methyl, Z is R^{30}-C wherein R^{30} is hydrogen and halogen, R^{31} is lower alkyl, halo-lower alkyl or C_3-C_7 cycloalkyl, R^{32} is lower alkyl, piperazinyl or lower alkyl-piperazinyl and R^{33} is hydrogen or halogen.

13. A compound as in claim 12 wherein R^{30} is hydrogen or fluorine, R^{31} is ethyl, fluoroethyl or cyclopropyl, R^{32} is methyl, 4-methyl-piperazinyl or piperazinyl and R^{33} is hydrogen or fluorine.

14. A compound as in claim 1 which is [6R-[6α,7β(Z)]]-7-[[(2-amino-4-thiazolyl)(R^{21}-oxyimino)acetyl]amino]-3-[[[[6-R^{33},8-R^{30}-1-(1-R^{31})-1,4-dihydro-7-(4-R^{34}-1-

piperazinyl)-4-oxo-3-quinolinyl]carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid and its pharmaceutically acceptable salts and hydrates of these acids and salts, wherein R^{33} and R^{30} is hydrogen or halogen, R^{31} is hydrogen, lower alkyl or halogen-lower alkyl, R^{34} is hydrogen or lower alkyl and R^{21} is the group



wherein R^{22} and R^{23} are selected from the group consisting of hydrogen and lower alkyl.

15. A compound as in claim 14 wherein R^{22} and R^{23} are both methyl.

16. A compound as in claim 15 wherein R^{33} and R^{30} are hydrogen and fluorine, R^{31} is ethyl or 2-fluoroethyl and R^{34} is methyl.

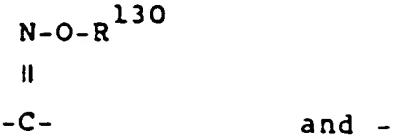
17. A compound as in claim 15 wherein R^{33} and R^{30} are fluorine, and R^{31} is 2-fluoroethyl.

18. A compound as in claim 14 wherein R^{33} is fluorine, R^{30} is fluorine, R^{31} is 2-fluoroethyl and R^{34} is methyl.

19. A compound as in claim 14 wherein R^{33} is fluorine, R^{30} is hydrogen, R^{31} is ethyl and R^{34} is methyl.

20. A compound as in claim 14 wherein R^{33} is fluorine, R^{31} is 2-fluoroethyl, R^{30} is hydrogen and R^{34} is methyl.

21. A compound as in any one of claims 8-20 wherein the



groupings are in the syn-form, i.e., the Z-form, or as mixtures in which the syn-form predominates.

22. A compound as in claim 1 which is [6R-[6α,7β(Z)]]-7-[[2-Amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[[[6,8-difluoro-1-(2-fluoroethyl)--1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinyl]-carbonyl]thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2--ene-2-carboxylic acid as well as salts of this compound and hydrates of this compound and salts.

23. Compounds as set forth in any one of claims 1-22 as pharmaceutically active substances.

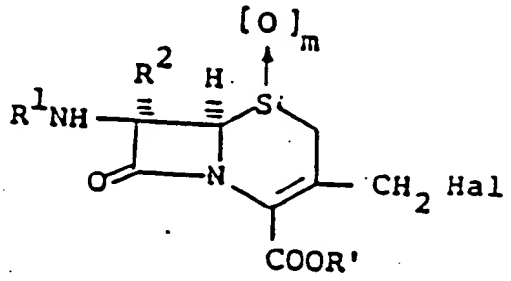
24. Compounds as set forth in any one of claims 1-22 as pharmaceutically active substances for the treatment and prophylaxis of infectious diseases.

25. A pharmaceutical preparation containing an acyl derivative according to any one of claims 1-22.

26. A pharmaceutical preparation for the treatment and prophylaxis of infectious diseases containing an acyl derivative according to any one of claims 1-22.

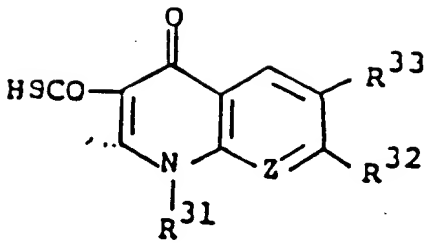
27. A process for the manufacture of the acyl derivatives according to any one of claims 1-22, which comprises

(a) for the manufacture of an easily hydrolyzable ester of a carboxylic acid of formula I reacting a compound of the formula



II

wherein m, R^1 and R^2 are as above, Hal is halogen and R' is the residue of an easily hydrolyzable ester, with a salt of a carbothioic acid of the formula

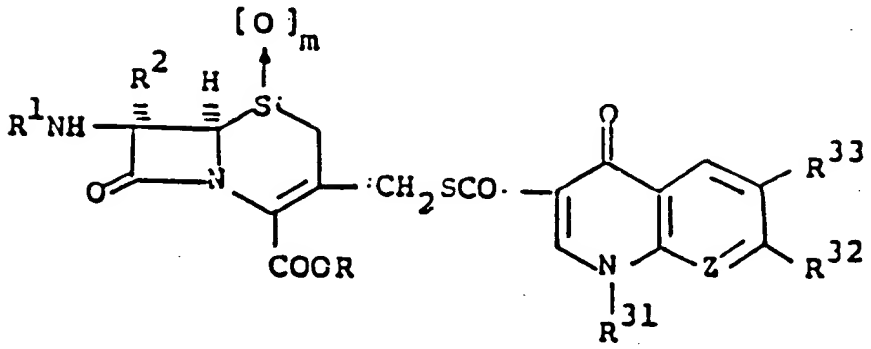


III

wherein R^{31}, R^{32} and R^{33} are as above,

or

(b) for the manufacture of a carboxylic acid of formula I converting an ester of the formula

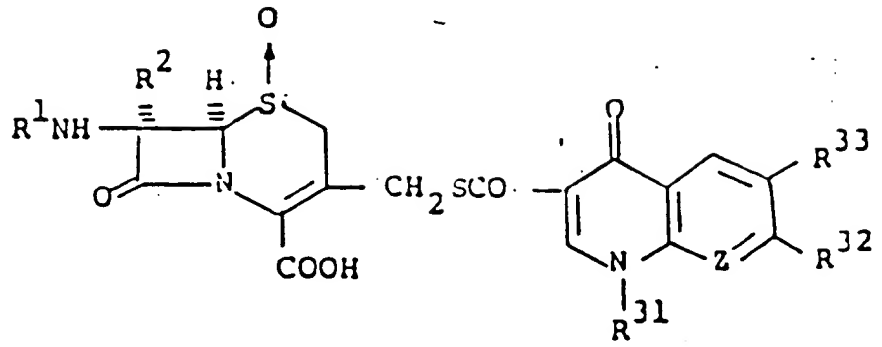


IV

wherein m, R^1, R^2, R^{31}, R^{32} and R^{33} are as above and R is an ester protecting group,

to the carboxylic acid of formula I, or

(c) for the manufacture of a compound of formula I, in which m is zero, reducing a compund of the formula

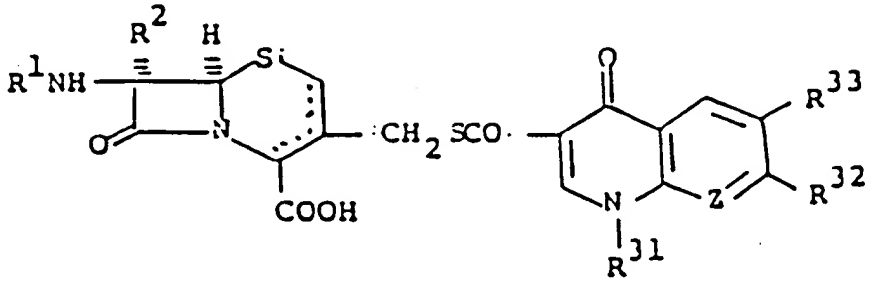


V

wherein R^1, R^2, R^{31}, R^{32} and R^{33} are as above,

or

(d) for the manufacture of a compound of formula I, in which m is 1 or 2, or an ester or salt thereof oxidizing a compound of the formula

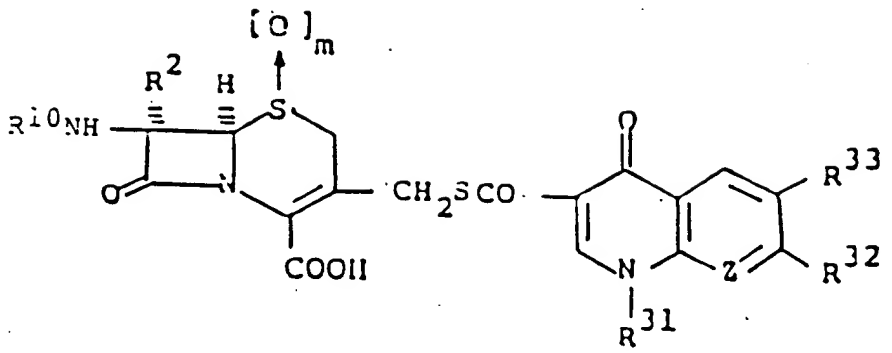


VI

wherein R^1, R^2, R^{31}, R^{32} and R^{33} are as above and the dotted lines indicate the presence of a Δ2 or Δ3 double bond,

or an ester or salt thereof, or

e) for the manufacture of a compound of formula I, in which R^1 contains an amino substituent, or an ester or salt thereof, cleaving off the amino-protecting group in the substituent R^{10} of a compound of the formula



VII

wherein m, R^2, R^{31}, R^{32} and R^{33} are as above and R^{10} is an acyl group containing a protected amino group,

or of an ester or salt thereof, or

(f) for the manufacture of a readily hydrolyzable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding esterification, or

(g) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts converting a compound of formula I into a salt or hydrate or into a hydrate of said salt.

28. Process according to claim 27, characterized in that one of the process alternatives (a), (b), (c) and (d) is carried out.

29. The use of the compounds according to any one of claims 1-22 in the treatment or prophylaxis of illnesses.

30. The use of the compounds according to any one of claims 1-22 in the treatment or prophylaxis of infectious diseases.

31. The use of the compounds according to any one of claims 1-22 for the manufacture of medicaments for the treatment or prophylaxis of infectious diseases.

32. Compounds according to any one of claims 1-21 whenever prepared according to the process claimed in claim 27 or 28 by an obvious chemical equivalent thereof.

33. The novel compounds, formulations, processes and methods substantially as described herein.

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DATED this EIGHTH day of DECEMBER 1988
F Hoffmann-La Roche & Co Aktiengesellschaft

Patent Attorneys for the Applicant
SPRUSON & FERGUSON